Remarks/Arguments

Claims 1-8, 10-11 and 15-19 are pending in the instant application. Claims 15-18 are withdrawn as being directed to non-elected subject matter. Applicants respectfully request that if a product claim(s) is found allowable, process claims that depend from or otherwise require all the limitations of the patentable product be rejoined with the allowable product claims.

The undersigned notes all references on the Information Disclosure Statement have been considered and that the restriction requirement has been made final.

The undersigned confirms that the subject matter of all claims was commonly owned at the time any inventions covered therein were made.

Applicants respectfully traverse the rejection of claims 1-7, 11 and 19 under 35 USC 103(a) as being unpatentable over *Beauchamp et al* (WO 02/08205).

The objective of the present invention is to provide new compounds useful as inhibitors of Tie2 activity. As remarked by the Examiner on page 9 of the Office Action, there is a recognized need for new Tie2 inhibitors.

The present invention concerns a relatively small group of compounds that are all structurally closely related. All of the presently claimed compounds exhibit six essential structural elements. Those six essential structural elements are: 1) a pyrimidine ring; 2) a 2-amino substitutent on the pyrimidine ring; 3) an alkynyl linker; 4) a ring A; 5) a linker group L; and 6) a ring B. All of these six features have been found to be essential for the Tie2 activity of the presently claimed compounds.

The Examiner suggests that the presently claimed invention is obvious over the disclosure of WO 02/08205 (*Beauchamp et al*). The scope and contents of Beauchamp are concerned only with new compounds for use in the treatment of neurodegenerative disorders. There is no mention of Tie2 inhibitory activity.

In *Beauchamp et al*, of the six essential structural elements of the present invention (listed above), only elements 1), 3) and 4) are always present in their compounds. Element 2) (the 2-amino substitutent on the pyrimidine ring) is disclosed, but not taught as essential. Element 4) is only partially disclosed in that the group X in *Beauchamp et al*, which is equivalent to ring A, may only be an aryl and not a heteroaryl group. Essential element 5) (the linker group L) is partially

disclosed in that the group X in *Beauchamp et al* may be substituted by a group y where y is NH-CO-R_4 where R_4 is (C1-6alkyl)aryl but the other values of the linker group L of the present invention are not disclosed. Also an equivalent of the linker group L is not taught as an essential feature as *Beauchamp et al* teaches that this feature can be omitted; of the 18 possible substituents listed in *Beauchamp et al* only one of those substituents gives rise to an equivalent of the linker group L of the present invention and in addition the substituent y is disclosed as an optional feature. Essential element 6) (ring B) is also only partially disclosed. The only substituent y on the group X in *Beauchamp et al* that gives rise to an equivalent of the ring B is where y is NH-CO-R_4 where R_4 is (C1-6alkyl)aryl; i.e. there may be an aryl substituent but not a heteroaryl group, nor a cycloalkyl nor a fully or partially saturated heterocyclic ring. Again an equivalent of the ring B is not taught as an essential feature; *Beauchamp et al* clearly teaches that this feature can be omitted. Therefore, Applicants submit it is clear that the contents of *Beauchamp et al* when taken as a whole do not make the compounds of the present invention structurally obvious.

To assist in determining the teaching of *Beauchamp et al* the preferences and examples of that document should be considered. In the preferences given on pages 7 to 12 of *Beauchamp et al*, no preference is given for R^4 being an alkyl aryl group. In addition there is no example of any compound having such a substituent in *Beauchamp et al*; such compounds are only generically disclosed therein. It is to be remembered that y only forms a linker group when it is substituted by R^4, where R^4 is an alkyl aryl group. All other options of R^4 and all other options of y are outside the scope of the present invention. There are no examples in *Beauchamp et al* of a compound having all six essential structural features of the compounds of the present invention. There are no examples in *Beauchamp et al* of a compound falling within the present claims. In the majority of the examples of *Beauchamp et al* y is absent, i.e. there is no substitution on the aryl ring X. Where there is a substitution, the group y is alkyl or halo. For all of these examples there are no equivalents of the essential structural Elements 5) (linker group L) or 6) (ring B) of the instant invention.

Applicants agree with the examiner that the closest compound in *Beauchamp et al* to the instant invention is the compound of Example 31, on page 35, which is listed as preferred, but not particularly preferred, on page 11 lines 19 to 20. In this compound y is 4-acetamido. There is no equivalent of the linker group L in this compound nor an equivalent of ring B. This compound is, therefore, at least two essential structural steps away from the presently claimed invention. The

Examiner suggests that the skilled person "would be motivated to pursue each of the limited possibilities taught by Beauchamp". Thus, the examiner contends it would be obvious to structurally modify the compound of Example 31 of *Beauchamp et al* by replacing the end hydrogen of the 4-acetamido group by an aryl group as this is one of the other options for R_4 listed in *Beauchamp et al*. Since neither the group R_4 nor the compound of Example 31 is in any way highlighted in *Beauchamp et al*, why would one of skill in the art be motivated to change that one substituent on that one specific compound over any other substituent on the compound of Example 31 or for that matter, over any subtituent on any other of the specifically disclosed compounds in *Beauchamp et al*. The Federal Circuit recently held that to prove prima facie obviousness for chemical cases based on structural similarity, "a showing that the prior art would have suggested making the specific [emphasis added] molecular modifications necessary to achieve the claimed invention is also required." [*Takeda Chem. Indus. et al. v. Alphapharm et al.*, No. 06-1329 (Fed. Cir. 2007, "Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."] Accordingly, contrary to the Examiner's position, since there is no suggestion to make the specific modification suggested by the Examiner, it is respectfully submitted the compounds of the instant invention are not obvious over *Beauchamp et al*.

Furthermore, when considering whether the present invention as a whole is obvious over *Beauchamp et al*, the utility of the compounds should be taken into consideration as the utility of the compounds forms a part of that invention as a whole. The activity of the compounds is not irrelevant as suggested by the Examiner. It would be irrelevant when determining the novelty of a group of compounds, but not when considering obviousness. The skilled person specifically searching for new Tie2 inhibitors upon reading the whole contents of *Beauchamp et al* would have no incentive to develop any of their compounds let alone one of their un-exemplified, non-preferred and non-specifically disclosed compounds. *Beauchamp et al* would not provide the skilled person with any expectation of success in finding compounds active as Tie2 inhibitors. There is nothing within *Beauchamp et al* or in the prior art relating to Tie2 inhibitors that would suggest the presently claimed group of compounds, most of which are many structural steps away from those of *Beauchamp et al*, would have Tie2 inhibitor activity. Furthermore, there is nothing within *Beauchamp et al* or in the prior art relating to Tie2 inhibitors that would suggest that replacement of the hydrogen group in Example 31 of *Beauchamp et al* with a 4-flouro substituted aryl group would lead to a compound having Tie2 inhibitory activity. The skilled

person would not consider a 4-flouro substituted aryl group to be the functional equivalent of hydrogen and in any case that skilled person would not expect the substitution of a hydrogen group with a 4-flouro substituted aryl group to convert a compound having activity in the treatment of neurodegenerative disorders into a compound having Tie2 inhibitor activity.
As the Examiner reasons on pages 9 and 10 of the Office Action, in the field of Tie2 inhibitors "minor structural changes can have significant impacts" on the activity of a compound even a "single modification" and that from the state of the art "it is highly unpredictable whether structurally related compounds will possess Tie2 inhibitory activity". Using this reasoning it is clear that the presently claimed compounds are not obvious over those of *Beauchamp et al*.
For the foregoing reasons, it is respectfully submitted that the difference between the present invention and *Beauchamp et al* are such that the subject matter of the present invention as a whole would not have been obvious to the person of ordinary skill in the art. Accordingly, it is respectfully requested that the rejection of claims 1-7, 11 and 19 under 35 USC 103(a) as being unpatentable over *Beauchamp et al* be reconsidered and removed.

Applicants respectfully traverse the rejection of claims 1-8, 10-11 and 19 under 35 USC 112, first paragraph, for failing to comply with the enablement requirement. The examiner argues that the instant invention is directed to "literally thousands of compounds" all of which are required to inhibit Tie2 kinase yet applicant provides in vitro data for only three. Examiner further states that "the nature of the invention is complex and, despite a recognized need for inhibitors of Tie2, there are few available. Moreover, among Tie2 inhibitors that have been developed, it is clear that minor changes can have significant impacts on their activity." The examiner concludes that "given the complex nature of the invention,…given the limited number of working examples,… and further given the unpredictability in the art" undue experimentation would be required to practice the invention as such the elected species in not enabled for inhibiting Tie2 activity.
Contrary to the Examiner's position, applicants contend that the presently claimed relatively small group of compounds, which are all closely structurally related, each of which possess the six essential structural elements described above, have Tie2 activity. The specification contains 153 specific examples ranging over the breadth of the claimed scope. In support of their position, Applicants are providing herewith IC_{50} data for each of the 153 exemplified compounds (including the elected species, i.e. example 22) indicating inhibition of autophosphorylation of Tie2 receptor tyrosine kinase I (See table below). The data is analogous to that given in Column 3 of Table A of the specification (page 85) for three of the exemplified compounds. This data demonstrates that Tie2 activity is possessed across the breadth of claimed scope.

Example Number	IC_{50} (μM) Inhibition of autophosphorylation of Tie2 receptor tyrosine kinase
1	0.2004
2	0.7396
3	0.0933
4	0.1340
5	0.1189
6	0.5327
7	0.0843
8	0.0631
9	1.3666
10	0.1332
11	0.0526
12	3.3757
13	1.0397
14	0.0414
15	0.2196
16	0.1006
17	0.5557
18	0.0002
19	0.3374
20	>16
21	2.6260
22	0.0003
23	1.2049
24	2.1520
25	0.0131
26	0.5395
27	0.0149
28	0.0157
29	0.1422
30	0.0740
31	0.1788
32	0.0444
33	2.5918
34	0.9471
35	0.4985
36	0.0568
37	0.0606
38	0.1374
39	0.0996
40	0.0150
41	0.1824
42	0.1292

43	0.2965
44	0.0180
45	0.3253
46	0.0305
47	0.0564
48	3.2873
49	0.9956
50	0.8447
51	0.8402
52	1.1486
53	0.1798
54	0.8740
55	6.5710
56	0.5424
57	1.1072
58	0.3706
59	0.2362
60	0.1848
61	0.3535
62	0.0324
63	0.4201
64	0.1974
65	0.0275
66	3.4090
67	1.5718
68	0.5735
69	0.2515
70	0.0797
71	0.0839
72	1.9045
73	0.0001
74	<0.0008
75	<0.0002
76	0.0123
77	0.2648
78	0.0173
79	0.0104
80	0.0274
81	0.6219
82	2.1150
83	0.0388
84	0.2470
85	<0.0005
86	0.0105
87	0.14191
88	0.01532

89	0.4485
90	0.00226
91	<0.0006
92	0.01293
93	0.06501
94	0.59349
95	0.58331
96	0.00466
97	0.02783
98	0.03776
99	0.02854
100	0.22292
101	0.40933
102	0.00914
103	0.08683
104	0.01035
105	0.09859
106	0.06998
107	0.02045
108	0.00713
109	1.85257
110	2.189
111	0.29175
112	0.50409
113	0.12653
114	0.03559
115	0.0961
116	0.27772
117	0.09944
118	0.02296
119	0.00966
120	0.09475
121	0.42909
122	1.18645
123	0.47209
124	0.15671
125	0.05137
126	0.09482
127	0.30467
128	0.2
129	1.1
130	0.15
131	0.03633
132	0.08551
133	0.29084
134	<0.0002

135	0.00969
136	0.28545
137	0.00422
138	0.0074
139	<0.0002
140	<0.0002
141	<0.0002
142	0.29202
143	0.25594
144	0.09831
145	0.01711
146	<0.0002
147	0.11667
148	0.02873
149	0.14408
150	1.2747
151	0.26452
152	0.88211

Accordingly, Applicants respectfully submit that claims 1-8, 10-11 and 19 are enabled for inhibiting Tie2 activity.

The provisional obvious-type double patenting rejections over copending application nos. 10/596,740, 11/185,182 and 11/815,269 are noted. Applicants would be willing to file any necessary terminal disclaimers if, and when, there is allowable subject matter, to overcome these rejections.

In view of the foregoing, Applicants believe the application is in condition for allowance, which action is respectfully requested.

Although Applicants believe no fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 101319-1P US.

Respectfully submitted,

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